TOBACCO INDUSTRY RESEARCH COMMITTEE
150 EAST FORTY SECOND STREET NEW YORK 17, N. Y.

#155 R1
(Activated 7/1/57)

Application For Research Grant

Date: April 14, 1953

1. Name of Investigator: Duane G. Wenzel, Ph.D.

2. Title: Professor of Pharmacology

3. Institution & Address: School of Pharmacy
University of Kansas
Lawrence, Kansas

4. Project or Subject: Further studies of the biological interaction between nicotine and hypercholesteralemia.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

The proposed study is to consist of two parts based upon observations made in prior work of the applicant. The observations related to the first proposal are as follows:
(a) Rabbits treated with a hypercholesterolemic diet plus nicotine (at all dosage levels) developed signs of peripheral vascular distrubances. These were manifest as reddening, alopecia localis, swelling and the development of severe lesions on all four paws. The symptoms progressed in the order named and were observed in three experimental groups receiving both nicotine and cholesterol, but were not observed in the control, cholesterol, or nicotine groups.
(b) The eyes of most of the cholesterol-nicotine animals developed cholesterol infiltration in both the sclera and the iris. The same effect, but apparently of a somewhat lesser intensity, was also observed with the cholesterol-only group.

On the basis of these two observations it is felt that the eye may be useful for the evaluation of the early deposition of cholesterol both in the sclera and iris and in the eyeground. It is anticipated that the time of onset and degree of involvement might be used to determine possible differences between the effects of hypercholesterolemia alone and with added nicotine. An ophthalmological camera is available, if necessary, to document any retinal effects. Three groups of female rabbits will be used for this study, a high cholesterol, a nicotine, and a nicotine-cholesterol group. To evaluate possible peripheral vascular disturbances the skin temperature of the extremities and that of the rectum will be measured with a thermistor thermometer to determine the thermal circulation index.

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It was further observed that the mortality of the hypercholesterolemic-nicotine-treated rabbits was significantly greater in two separate studies than that of the hypercholesterolemic or nicotine groups. These latter groups were essentially intact at the conclusion of the studies while the majority of the nicotine-hypercholesterolemic animals were dead. This lethal interaction was not readily apparent with chickens.

It is proposed that rats be used to determine the possible species relationship of this effect and the resultant pathology. Three groups of male rats are to be used as in the other portion of the proposal relating to rabbits. The groups of rats are to be at least 20 each and are to be housed in separate cages. Hypercholesterolemia will be induced according to the procedure of Vitale et al. (1) The pathology will be determined by Dr. James Turner.

The amount of nicotine to be used in both studies will be the equivalent of two packs of cigarettes daily in terms of average nicotine absorption by man and body weight. This amount per se in previous studies with rabbits and chickens was found to have no demonstrable effect on the mortality rate or pathology.

(1) Vitale, J.J., White, P.L., Nakamura, M., Hegsted, D.M., Zamcheck, N., and Hellerstein, E.E., J. Exp. Med., 106, 757 (1957)

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6. Budget Plan:

Salaries	5,200.00
Expendable Supplies	600.00
Permanent Equipment	700.00
Overhead	1,005.00
Other (15%) (Travel)	200.00
Total	7,705.00

As expenses will be greatest at the initiation of the work, it is requested that the amount be made available immediately rather than in quarterly payments.

7. Duration of Work:

8. Calendar year July 1, 1958 through June 30, 1959

An air-conditioned animal room and completely equipped research laboratories are available for this project. The project director will be available on a full-time basis for two months of the summer and on a part-time basis during the remainder of the year. A one-half time research associate will work on the project throughout the year. Other personnel whose services will be used include: a pathologist, laboratory technician, animal room caretaker, biometrician and others. Specialized equipment in the Department of Pharmacology includes Addenbrooke's manometer apparatus, spectrophotometer, oscilloscope and recorder, oscillograph, amplifiers, preamplifiers, stimulators, flame photometer, etc.

9. None

10. Additional Information (Including relation of work to other projects and other sources of supply):

The proposed study is based upon results of a previous experiment with rabbits to be published in the J. Am. Pharm. Assoc., Sci. Ed. March, 1958; a similar project completed with chickens; and a project using rabbits and now being supported by the Tobacco Industry Research Committee.

Signature /s/ Dunne G. Venzel
Director of Project

/s/ William J. Ruerdinger, Jr.
Business Officer of the Institution

Associate Dean, Graduate School

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